ANIMAL MODELS OF **ORGAN-SPECIFIC** TOLERANCE FOR HEART AND LUNG TRANSPLANTATION

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PARTICIPATING INSTITUTES AND CENTERS (ICs):

National Heart, Lung, and Blood Institute (NHLBI)
(http://www.nhlbi.nih.gov)

THIS PA CONTAINS THE FOLLOWING INFORMATION:

PURPOSE OF THIS PA

The purpose of this Program Announcement (PA) is to encourage the submission of applications for the development **organ-specific** tolerance protocols using 1) large animal models for heart transplantation, and 2) both large and small animal models for lung transplantation. The long-range goal is to provide animal models that may be used for preclinical studies of immune tolerance induction, specifically in heart or lung studies, and improve the long-term quality of life and survival of recipients of heart and lung transplants.

RESEARCH OBJECTIVES

Transplantation is the only successful therapy for end-stage heart or lung failure. While the current one-year survival rate for heart and lung transplant recipients (85% and 77% respectively) is very good, it depends on life-long use of drugs powerful enough to prevent the immune system from rejecting the transplanted **organ**. Moreover, long-term use causes nephrotoxicity and increased susceptibility to serious infections and malignancies. In addition, although immunosuppressive agents are relatively effective at preventing acute **rejection**, patients still frequently develop chronic **rejection**. Chronic **rejection** in heart transplants, manifested as transplant allograft vasculopathy, is the primary cause of the low five-year

survival' (68%) in patients who escape acute **rejection**. In lung transplants, chronic **rejection** presents as obliterative bronchiolitis, which is the main factor contributing to the dismal 44% five-year survival for lung transplant recipients.

All transplant patients would benefit enormously if a state of **specific** immune tolerance could be induced. The induction of tolerance could greatly reduce the medical, personal, and economic burden of immunosuppressive therapy as well as the high mortality associated with chronic **rejection**. Indeed, selective suppression of immunity to "non-self" antigens on the transplanted **organ** with retention of normal immune function is the ultimate goal of transplantation immunology.

In rodent models, numerous strategies have been used successfully to induce tolerance to heart transplantation. However, in terms of heart transplantation, these strategies have not been reproducible in large animal models, such as non-human primates or miniature swine. Although the rodent is an economical model for identifying strategies of tolerance induction, its immune system may be too different from that of the human to serve as a pre-clinical model. For example, 1) the age-related decline in T **cell** regeneration is much greater in humans than in mice, 2) the role of the interleukin receptor common ? chain differs between mice and primates; and 3) B **cell** and T **cell** development responds to different regulatory factors in these two species. Ethical considerations require a more suitable pre-clinical model to more accurately predict how the protocol will work in humans. Thus, a large animal model, with an immune system more reflective of the human immune system, is essential for testing heart and lung tolerance protocols before moving into clinical studies. The primary focus for immune tolerance in lung transplantation at present, however, is to develop protocols in small animal models that can be moved into large animals.

This PA seeks to encourage multidisciplinary research that will focus on elucidating methods and mechanisms of antigen-**specific** tolerance induction and maintenance in clinically relevant animal transplant models. Both small and large animal models are appropriate for studies investigating tolerance in the lung. Heart studies should use only large animal models. Human studies are not appropriate for the scope of this PA. **Specific** examples of areas of research interest may include, but are not restricted to, the following:

o Definition and manipulation of **specific** immune pathways involved in the induction and maintenance of antigen-**specific** tolerance, including: co-stimulatory pathways, cytokine modulation, the role of adhesion molecules, and leukocyte migration.

o Identification of allo-reactive lymphocytes subsets and their correlation with functions such as inflammation, homing and migration.

o Determination and validation of biomarkers of antigen-**specific** immune tolerance.

o Studies of the genetics of tolerance induction and long-term maintenance of tolerance.

o Elucidation of the molecular, biochemical and cellular mechanisms involved in the loss of antigen-**specific** tolerance.

o Use of very young animals to determine whether it is easier to induce tolerance in a young animal before the immune system is mature.

MECHANISM(S) OF SUPPORT

This PA will use the NIH research project grant (R01) award mechanism. As an applicant, you will be solely responsible for planning, directing, and

executing the proposed project. The total project period for an application submitted in response to this PA may not exceed five years.

This PA uses just-in-time concepts. It also uses the modular as well as the non-modular budgeting formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular format. Otherwise follow the instructions for non-modular research grant applications.

ELIGIBLE INSTITUTIONS

You may submit (an) application(s) if your institution has any of the following characteristics:

o For-profit or non-profit organizations
o Public or private institutions, such as universities, colleges, hospitals, and laboratories
o Units of State and local governments
o Eligible agencies of the Federal government
o Domestic or foreign

INDIVIDUALS ELIGIBLE TO BECOME PRINCIPAL INVESTIGATORS

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

WHERE TO SEND INQUIRIES

We encourage your inquiries concerning this PA and welcome the opportunity answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

o Direct your questions about scientific/research issues to:

For heart transplantation:

Judith Massicot-Fisher, PhD
Division of Heart and Vascular Disease
National Heart, Lung, and Blood Institute
Rockledge II, Room 9184
Bethesda, MD 20892-7940
Telephone: (301) 435-0528
FAX: (302) 480-1454
E-mail: Massicoj@nih.gov

For lung transplantation:

Dorothy Gail, Ph.D.
Program Director
Lung Biology and Diseases Program
Division of Lung Diseases
National Heart, Lung and Blood Institute
Rockledge II, Room 10100
Bethesda, MD 20892-7952
Telephone: (301) 435-0222
FAX: (301) 480-3557
E-mail: GailD@nih.gov

o Direct your questions about financial or grants management matters to:

Ms. Tanya McCoy
Division of Extramural Affairs
National Heart, Lung, and Blood Institute
Rockledge II, Room 7154
Bethesda, MD 20892-7926
Telephone: (301) 435-0171
FAX: (301) 480-3310
Email: McCoyT@nih.gov

SUBMITTING AN APPLICATION

Applications must be prepared using the PHS 398 research grant application instructions and forms (rev. 5/2001). The PHS 398 is available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

APPLICATION RECEIPT DATES: Applications submitted in response to this program announcement will be accepted at the standard application deadlines, which are available at http://grants.nih.gov/grants/dates.htm. Application deadlines are also indicated in the PHS 398 application kit.

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS: Applications requesting up to $250,000 per year in direct costs must be submitted in a modular grant format. The modular grant format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in $25,000 modules. Section C of the research grant application instructions for the PHS 398 (rev. 5/2001) at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular grants. Additional information on modular grants is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

SPECIFIC INSTRUCTIONS FOR APPLICATIONS REQUESTING $500,000 OR MORE PER YEAR: Applications requesting $500,000 or more in direct costs for any year must include a cover letter identifying the NIH staff member within one of NIH institutes or centers who has agreed to accept assignment of the application. NHLBI 'Guidelines for Applications with Direct Costs of $500,000 or More in Any One Year' may be found at: http://www.nhlbi.nih.gov/funding/policies/500kweb.htm.

Applicants requesting more than $500,000 must carry out the following steps:

1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Identify, in a cover letter sent with the application, the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

SENDING AN APPLICATION TO THE NIH: Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review

National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710
Bethesda, MD 20817 (for express/courier service)

APPLICATION PROCESSING: Applications must be received by or mailed before the receipt dates described at http://grants.nih.gov/grants/funding/submissionschedule.htm. The CSR will not accept any application in response to this PA that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The CSR will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

PEER REVIEW PROCESS

Applications submitted for this PA will be assigned on the basis of established PHS referral guidelines. An appropriate scientific review group convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

o Receive a written critique
o Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score
o Receive a second level review by the appropriate national advisory council or board

REVIEW CRITERIA

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments, reviewers will be asked to discuss the following aspects of your application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals:

o Significance
o Approach
o Innovation
o Investigator
o Environment

The scientific review group will address and consider each of these criteria in assigning your application's overall score, weighting them as appropriate for each application. Your application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, you may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) SIGNIFICANCE: Does your study address an important problem? If the aims of your application are achieved, how do they advance scientific knowledge? What will be the effect of these studies on the concepts or methods that drive this field?

(2) APPROACH: Are the conceptual framework, design, methods, and analyses adequately developed, well integrated, and appropriate to the aims of the project? Do you acknowledge potential problem areas and consider alternative tactics?

(3) INNOVATION: Does your project employ novel concepts, approaches or methods? Are the aims original and innovative? Does your project challenge existing paradigms or develop new methodologies or technologies?

(4) INVESTIGATOR: Are you appropriately trained and well suited to carry out this work? Is the work proposed appropriate to your experience level as the principal investigator and to that of other researchers (if any)?

(5) ENVIRONMENT: Does the scientific environment in which your work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

ADDITIONAL REVIEW CRITERIA: In addition to the above criteria, your application will also be reviewed with respect to the following:

PROTECTIONS: The adequacy of the proposed protection for humans, animals, or the environment, to the extent they may be adversely affected by the project proposed in the application.

BUDGET: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research.

AWARD CRITERIA

Applications submitted in response to a PA will compete for available funds with all other recommended applications. The following will be considered in making funding decisions:

o Scientific merit of the proposed project as determined by peer review
o Availability of funds
o Relevance to program priorities

REQUIRED FEDERAL CITATIONS

PUBLIC ACCESS TO RESEARCH DATA THROUGH THE FREEDOM OF INFORMATION ACT: The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm.

Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget justification section of the application.

URLs IN NIH GRANT APPLICATIONS OR APPENDICES: All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

HEALTHY PEOPLE 2010: The Public Health Service (PHS) is committed to

achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople.

AUTHORITY AND REGULATIONS: This program is described in the Catalog of Federal Domestic Assistance No. 93.837 and 93.838 and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and administered under NIH grants policies described at http://grants.nih.gov/grants/policy/policy.htm and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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Department of Health and Human Services

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